

NEW DRUG UPDATE

Drug Name:	rivaroxaban
Trade Name (Manufacturer):	Xarelto® (Janssen)
Form:	Tablets, Immediate-release
Strength:	10 mg
FDA Approval:	July 1, 2011
Market Availability:	Available
FDA Approval Classification:	Standard review
Classification:	Specific Therapeutic Class (HIC3): Pending

Indication:¹ Rivaroxaban (Xarelto), a direct factor Xa inhibitor, is indicated for the prevention of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.

Contraindications/Warnings: Rivaroxaban is contraindicated in patients with hypersensitivity to the product and in patients with active major bleeding.

Rivaroxaban increases risk of bleeding and can cause serious or fatal bleeding. It should be used with caution in pregnancy due to potential obstetric hemorrhage and/or emergent delivery. Patients should be evaluated for signs and symptoms of blood loss. Rivaroxaban increases the risk of epidural or spinal hematoma. Epidural catheters should not be withdrawn earlier than 18 hours after the last rivaroxaban dose and the next dose should be held for at least six hours post removal. Withhold rivaroxaban for 24 hours after traumatic epidural or spinal puncture.

Drug Interactions: Avoid concomitant use with combined p-glycoprotein (P-gp) and strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) as they increase rivaroxaban concentrations. In patients with renal impairment on concomitant combined p-glycoprotein (Pg) and strong CYP3A4 inhibitors (e.g. amiodarone, diltiazem, dronedarone, felodipine, macrolides, quinidine, ranolazine, verapamil) avoid use unless the benefit outweighs the bleeding risk, since these patients may be at increased bleeding risk. With combined P-gp and strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's wort) avoid concomitant use or consider increasing the rivaroxaban dose to 20 mg once daily with food. Avoid use with other drugs that affect hemostasis such as anticoagulants, fibrinolytics, NSAIDs/aspirin, and antiplatelet drugs. Avoid concomitant use with clopidogrel unless the benefit outweighs the bleeding risk.

Common Adverse Effects: The most common adverse event is bleeding. In clinical trials the risk of bleeding was similar to that of enoxaparin (Lovenox) 40 mg once daily. Major bleeding was seen in less than one percent of patients (for both hip and knee replacement surgery).

During rivaroxaban treatment, the majority of major bleeding complications (≥60 percent) occurred during the first week after surgery.

Alanine aminotransferase (ALT) greater than three times the upper limit of normal (ULN) was seen in 2.6 percent versus 3.8 percent of patients on rivaroxaban versus enoxaparin in RECORD 1-3.

Special Populations:

Pediatrics: The safety and effectiveness of rivaroxaban in pediatrics has not been established.

Pregnancy: Pregnancy Category C. Rivaroxaban dosing in pregnancy has not been studied.

Geriatrics: In clinical trials, no overall differences in effectiveness or safety were reported between patients < 65 years and those > 65 years of age. However, the elderly subjects exhibited an increase in drug exposure that may be caused by age-related changes in renal function.

Renal Impairment: Rivaroxaban is not recommended in patients with severe renal impairment (CrCL <30 mL/min). It should be used with caution in patients with moderate renal impairment (CrCL 30 mL/min to 49 mL/min). Discontinue rivaroxaban if acute renal failure develops.

Hepatic Impairment: Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease with coagulopathy.

Dosage: The recommended dosage of rivaroxaban is 10 mg orally once daily without regard to food, starting six to ten hours post-op, after hemostasis has been established. The duration of treatment for hip and knee replacement is 35 days and 12 days, respectively. Missed doses should be taken as soon as possible, on the same day and continued on the following day, with the usual once daily administration.

The absorption of rivaroxaban is dependent on the site of drug release in the gastrointestinal (GI) tract (gastric versus small intestine or colon). Absorption is decreased significantly if given using a feeding tube which deposits drug in the proximal small intestine or further down the GI track. If a feeding tube is used for administration, confirm gastric placement.

Clinical Trials: A literature search was performed using “rivaroxaban” and “deep vein thrombosis” and “pulmonary embolism” and “hip surgery” and “knee surgery”.

Three studies led to the FDA-approval of rivaroxaban: Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) 1 and 2 (n=6,727) for elective total hip replacement and RECORD 3 (n=2,531) for elective total knee replacement.² All three were randomized, double-blind, multinational trials that compared oral rivaroxaban 10 mg once daily started 6-8 hours after wound closure to subcutaneous (SC) enoxaparin 40 mg once daily started 12 hours pre-op. Enoxaparin 40 mg once daily is not the FDA-approved dose in knee replacement. In all these trials, rivaroxaban was superior in preventing total venous thromboembolism (VTE) (a composite endpoint of DVT, nonfatal PE, and death from any cause) and major VTE (a composite endpoint of proximal DVT, nonfatal PE, and venous thromboembolic death).

In RECORD 1 and 2, a total of 6,727 patients were randomized and 6,579 received study drug. In RECORD 1, the mean exposure duration (± SD) to rivaroxaban and enoxaparin was 33.3 + 7 and 33.6 + 8.3 days, respectively. In RECORD 2, the mean exposure duration to rivaroxaban and enoxaparin was 33.5 + 6.9 and 12.4 + 2.9 days, respectively. After Day 13, oral placebo was continued in the enoxaparin group for the remainder of the double-blind study duration.

In RECORD 1, the occurrence of the primary efficacy outcome of total VTE at 36 days was 1.1 percent for rivaroxaban and 3.7 percent for enoxaparin ($p < 0.001$; absolute risk reduction 2.6%; 95% CI, 1.5 to 3.7, number needed to treat [NNT]=38).³ The main secondary outcome of major VTE occurred in 0.2 percent of patients in the rivaroxaban group and in two percent of patients in the enoxaparin group ($p < 0.001$, absolute risk reduction 1.7 percent, 95% CI, 1 to 2.5). The primary safety outcome of major bleeding occurred in 0.3 percent and 0.1 percent of patients in the rivaroxaban and enoxaparin groups respectively ($p = 0.18$).

In RECORD 2, the occurrence of the primary efficacy outcome of total VTE in the rivaroxaban versus enoxaparin groups was two percent versus 8.4 percent ($p < 0.001$, absolute risk reduction 7.3 percent, 95% CI, 5.2 to 9.3, NNT=14).⁴

In RECORD 3, the mean exposure duration (\pm SD) to rivaroxaban and enoxaparin was 11.9 + 2.3 and 12.5 + 3 days, respectively.⁵ The primary outcome of total VTE 13 to 17 days after surgery occurred in 9.6 percent and 18.9 percent of patients treated with rivaroxaban and enoxaparin, respectively ($p < 0.001$, absolute risk reduction 9.2 percent, 95% CI, 5.9-12.4, NNT=11). The secondary outcome of major VTE occurred in one percent of patients in the rivaroxaban group and 2.6 percent of patients in the enoxaparin group ($p = 0.01$, absolute risk reduction 1.6 percent, 96% CI, 0.4-2.8). The primary safety outcome of major bleeding occurred in 0.6 percent and 0.5 percent of rivaroxaban- and enoxaparin-treated patients, respectively.

RECORD 4 ($n = 3,148$) was a randomized, double-blind study comparing oral rivaroxaban 10 mg once daily to SC enoxaparin 30 mg every 12 hours (FDA-approved dose for knee replacement) in patients undergoing total knee replacement surgery.⁶ The primary outcome (composite of DVT, PE, or death from any cause up to day 17 after surgery, occurred in 6.9 percent compared to 10.1 percent patients on rivaroxaban and enoxaparin, respectively ($p = 0.0118$, absolute risk reduction 3.19 percent, 95% CI, 0.71-5.67, NNT=31). Major bleeding occurred in 0.7 percent of rivaroxaban patients compared with 0.3 percent of enoxaparin patients.

Other Drugs Used for Condition: Drugs FDA-approved for prevention of DVT/PE in patients undergoing elective hip and knee replacement surgery include: SQ unfractionated heparin sodium, a low molecular weight heparin (LMWH) SC enoxaparin (Lovenox[®]) and fondaparinux (Arixtra[™] and generic). Injectable dalteparin (Fragmin), another LMWH, is FDA-approved for DVT prophylaxis in hip replacement surgery. Oral warfarin (Coumadin[®] and generic) is indicated for prophylaxis and/or treatment of thrombosis and its extension and PE, but not specifically for prevention of DVT/PE following hip or knee replacement. However, treatment guidelines recommend the use of oral warfarin (Coumadin and generic) as one of the therapeutic choices. The Eighth American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines were published in 2008 therefore does not address rivaroxaban.⁷

Place in Therapy: In comparative studies, the oral anticoagulants rivaroxaban (Xarelto) has shown superiority to enoxaparin prevention of DVT/PE in elective hip and knee replacement surgery. The safety profile of rivaroxaban appears to be similar to that of enoxaparin in this orthopedic population. Rivaroxaban does not require laboratory monitoring or have food interactions. The half-life of rivaroxaban is five to 13 hours. It does not have a specific antidote. Rivaroxaban offers a once-daily oral option for DVT/PE prophylaxis in hip and knee replacement surgery.

References

¹ Xarelto [package insert]. Titusville, NJ; Janssen; July 2011.

² Xarelto [package insert]. Titusville, NJ; Janssen; July 2011.

³ Eriksson BI, Borris LC, Friedman RJ, et al. RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *J Engl J Med*. 2008; 358(26):2765-2775.

⁴ Kakkar AK, Brenner B, Dahl OE, et al. RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind randomised controlled trial. *Lancet*. 2008; 372(9632):31-39.

⁵ Lassen MR, Ageno W, Borris LC, et al. RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008; 358(26):2776-2786.

⁶ Turpie AG, Lassen MR, Davidson BL, et al. RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet*. 2009; 373(9676):1673-1680.

⁷ Hirsh J, Guyatt G, Albers GW, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008; 133(6S):71S-109S.